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New biphenylic derivatives: synthesis, characterisation and enantiodiscrimination in chiral aggregates

Romana Andreani,[a] Cecilia Bombelli,[a] Stefano Borocci,[b] Juri Lah,[c] Giovanna Mancini,[d,*] Paolo Mencarelli,[a] Gorazd Vesnaver[c] and Claudio Villani[e]

[a]*Dip. di Chimica Università degli Studi di Roma 'La Sapienza', P.le A. Moro 5, 00185 Roma, Italy*
[b]*Dipartimento di Scienze Ambientali, Università della Tuscia, Largo dell' Università, 01100 Viterbo, Italy*
[c]*Department of Chemistry, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia*
[d]*CNR Istituto di Metodologie Chimiche Sezione Meccanismi di Reazione c/o dip. Chimica Università degli Studi di Roma 'La Sapienza', P.le A. Moro 5, 00185 Roma, Italy*
[e]*Dip. di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive Università degli Studi di Roma 'La Sapienza', P.le A. Moro 5, 00185 Roma, Italy*

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Abstract—Chiral discrimination of racemic 2,2′-diamino-6-(octanoyloxymethyl)biphenyl and 2,3′-diamino-6-(octanoyloxymethyl)biphenyl in micelles formed either by *N*-alkyl-*N,N*-dimethyl-*N*-(*S*)-(1-phenyl)ethylammonium bromide or sodium *N*-dodecanoyl-L-prolinate has been investigated by ^{1}H NMR spectroscopy. The rotational barrier of 2,3′-diamino-6-(octanoyloxymethyl)biphenyl has been evaluated by HPLC and by dynamic NMR. The rotational barrier of 2,3′-diamino-6-(acetoxymethyl)biphenyl was evaluated by theoretical calculations and compared with the experimental data relative to its analogue.

1. Introduction

The study of chiral recognition in micellar aggregates is of interest in many research fields. Micelles are in fact very simple models of biomembranes and the identification of non-covalent interactions responsible for chiral recognition in these aggregates may be of help in clarifying some of the recognition phenomena responsible for membrane organisation. These same interactions might also have played some role in the homochirality of biomolecules either in the breaking of symmetry[1] or in the amplification of a first enantiomeric imbalance.[2] The increasing demand of enantiopure molecules[3] stimulates, besides enantioselective synthesis, new methods both for enantioseparation and for enantiopurity determination. The knowledge of the non-covalent interactions responsible for chiral recognition could address the preparation of new chiral selective molecules. The use of atropoisomeric compounds characterised by a relatively low rotational barrier is very useful in this kind of investigation[4] because the preferential interactions of one of the enantiomers with chiral aggregates may be revealed by a deracemisation process. Moreover, the racemic mixture of some of these atropoisomeric compounds is more accessible than enantiopure molecules.

Herein we report an ^{1}H NMR investigation carried out in aqueous solution of racemic 2,2′-diamino-6-(octanoyloxymethyl)biphenyl **1a** and 2,3′-diamino-6-(octanoyloxymethyl)biphenyl **2a** in the presence of aggregates formed either by an anionic surfactant, sodium *N*-dodecanoyl-L-prolinate **3**, or cationic surfactants *N*-alkyl-*N,N*-dimethyl-*N*-(*S*)-(1-phenyl)ethylammonium bromide **4** (alkyl = C_{12}, **4a**; alkyl = C_{16}, **4b**). We also report the evaluation of the rotational barrier of 2,3′-diamino-6-(octanoyloxymethyl)biphenyl **2a** by dynamic NMR experiments carried out in the presence of chiral aggregates and by dynamic HPLC on a chiral phase. The rotational barrier of a simpler analogue of the biphenylic derivative **2a**, namely 2,3′-diamino-6-(acetoxymethyl)biphenyl **2b**, was evaluated by theoretical calculation.

The anionic chiral surfactant **3** has been studied extensively in our laboratory and has been shown to be

* Corresponding author. Tel.: +39-0649913078; fax: +39-06490421; e-mail: gmancini@uniroma1.it

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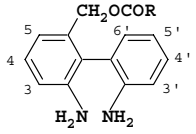
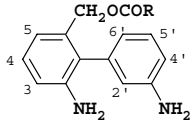
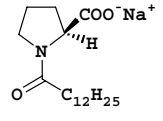
characterised by a high extent of organisation[5] and to be able to discriminate the enantiomers of biarylic derivatives.[6] Cationic surfactants **4** have been used as media for diastereoselective reactions[7] but, to the best of our knowledge, have not been investigated in the deracemisation of atropoisomeric compounds. Their advantages are both the presence of an aromatic ring, that could give π-stacking interactions with the solute, and the commercial availability of both the enantiomers of *N,N*-dimethyl-α-methylbenzylamine, which upon alkylation yield the cationic surfactants **4**. The possibility of an easy preparation of both enantiomers of a chiral surfactant is in fact an important point in this kind of investigations.



1a, R=C_7H_{15}
1b, R=CH_3



2a, R=C_7H_{15}
2b, R=CH_3



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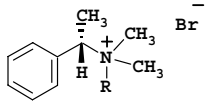

4a, R=$C_{16}H_{33}$
4b, R=$C_{12}H_{25}$

2. Results and discussion

The chiral surfactants were prepared and purified according to described procedures[5,8] and then fully characterised as reported in the experimental section. The Krafft point[9] and cmc[10] of surfactants **4** were measured according to reported procedures. Isothermal titration microcalorimetry (ITC) experiments, carried out for the measurement of the cmcs also yielded the thermodynamic parameters of the micellisation of **4a** and **4b** (Table 1), derived on the basis of the mass action model of the micellisation process.[10a,c,d]

From Table 1 it is evident that micellisation of both surfactants is an entropy driven process in which high entropy contributions ($T\Delta S^{o}_{M}$) can be attributed to the release of the hydrophobically structured water around the alkyl chains that accompanies the micellisation process. Similarly, the more positive $T\Delta S^{o}_{M}$ contribution observed with **4a** can be ascribed to the larger amount of hydrophobically structured water released upon micellisation. The more favourable (exothermic) ΔH^{o}_{M} contribution can be attributed to the higher number of van der Waals contacts formed during the aggregation of the longer chains of **4a**. All thermodynamic parameters determined for **4b** and **4a** agree well with the corresponding values of cmc, ΔG^{o}_{M}, ΔH^{o}_{M} and $T\Delta S^{o}_{M}$ for alkylpyridinium bromides and alkyltrimethylammonium bromides of the same chain length.[15,19]

Table 1. Thermodynamic parameters[a] of micellisation for **4a** and **4b** at 398 K obtained from isothermal titration microcalorimetry[10a]

Surfactant	cmc, mmol kg^{-1}	ΔG^{o}_{M},[b] kJ mol^{-1}	ΔH^{o}_{M}, kJ mol^{-1}	$T\Delta S^{o}_{M}$, kJ mol^{-1}
4a	0.24	−55.1	−8.7	46.4
4b	7.7	−39.6	−3.1	36.5

[a] The relative errors in ΔG^{o}_{M}, ΔH^{o}_{M} and $T\Delta S^{o}_{M}$ ($\Delta H^{o}_{M} - \Delta G^{o}_{M}$) are estimated to be about 2%, 10% and 2%, respectively.

[b] ΔG^{o}_{M} values were calculated using $p/n = 0.2$, which is a characteristic value for C_{12} and C_{16} analogue alkylpyridinium bromides.[10e]

The biphenylic derivatives were prepared by Ulmann coupling of 2-bromo-3-nitromethylbenzoate with 1-iodo-2-nitrobenzene or 1-iodo-3-nitrobenzene (for the preparation of compounds **1a** and **2a**, respectively).

The enantiomers of the two biphenylic derivatives were resolved by HPLC on an amylose carbamate chiral stationary phase. In the case of compound **1a**, two well resolved peaks were observed in the chromatograms at temperatures in the range 298–318 K; evidence of a stability towards enantiomer interconversion that allowed us to characterise one of the enantiomers by CD spectroscopy (Fig. 1).

The absence of peak broadening or plateau-like regions (see further) in the chromatograms of **1a** is consistent with slow *R*/*S*-enantiomerisation on the time scale of the HPLC separation, as expected for a tri-*ortho* substituted biphenyl with medium sized substituents.[11]

Under the same HPLC conditions, compound **2a** yielded a single peak at temperatures near or above 298 K. When the column temperature was lowered in 5 K steps, the peak progressively broadened and eventually split into two peaks with a plateau-like region between them at a column temperature of 268 K (Fig. 2). This behaviour is consistent with enantiomer interconversion becoming increasingly slower on the HPLC time scale.

Computer simulation of the exchange-broadened elution profile obtained at 268 K (Fig. 2), gave the averaged

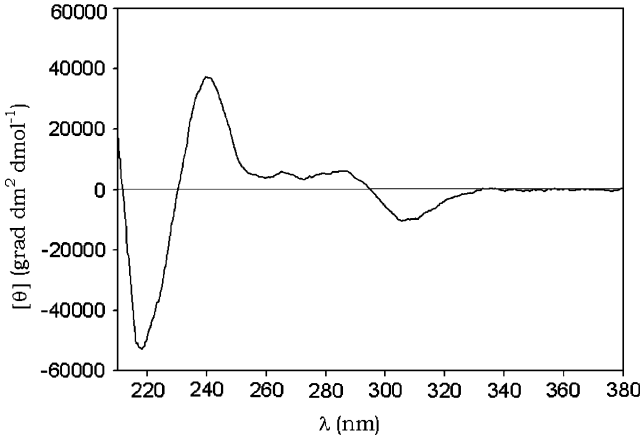

Figure 1. CD spectrum of biphenylic derivative **1a** in EtOH.

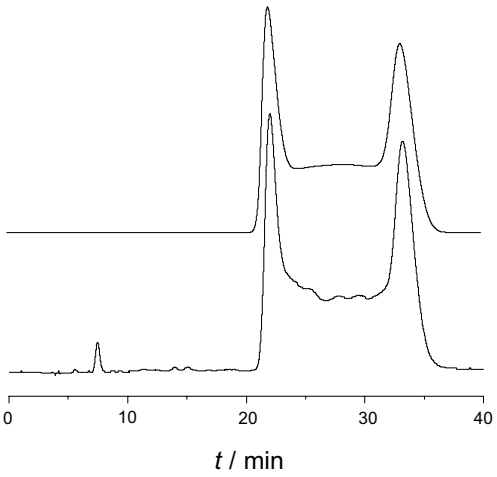

Figure 2. Experimental (bottom) and simulated (top) chromatograms of **2a** on a chiral stationary phase. Experimental: Chiralpak AD 250×4.6 mm i.d. column; eluent hexane/isopropanol 80/20; temperature 268 K; flow rate 1.0 mL/min; UV at 254 nm. Simulated: $N_1 = 1370$; $N_2 = 1426$; $k_m = 0.15\,min^{-1}$.

apparent rate constant for the enantiomer interconversion and the corresponding energy barrier $\Delta G^{\#}_{268} = 19.7 \pm 0.2\,kcal\,mol^{-1}$.[12]

The rotational barrier of biphenylic derivative **2a** was evaluated under aggregating conditions by dynamic NMR.

Coalescence of the diastereomeric signals due to aromatic protons at the 2′ position was observed at 363 K. This temperature and the value of the rate of enantiomerisation at the coalescence temperature $k_c = 77.0\,s^{-1}$ obtained by Eq. 1 were used in the Eyring equation[13] and yielded $\Delta G^{\#}_{363} = 18.3 \pm 0.2$ kcal mol^{-1} for the rotational barrier.

$$k_c = 2.22\Delta v \qquad (1)$$

2.1. Theoretical calculation

In a previous paper we showed that the rotational barrier of a substituted biphenyl can be reliably evaluated by DFT calculations at the B3LYP/6-31G(d) level of theory.[14] The results obtained at such a level of theory were almost coincident with those obtained at the higher B3LYP/6-311+G(d,p) level of theory. Furthermore, the results from the DFT calculations were in good agreement with those obtained at the MP2/6-31G(d) level of theory. Our observation of the good behaviour of the DFT approach was in accordance with results obtained by other authors in the calculations of rotational barriers in biphenyls.[15]

Therefore, the same DFT approach was used herein and the calculations for the rotational barrier of **2b** were carried out with both basis sets in order to verify if, also in this case, the results obtained with the smaller one were coincident with those obtained with the larger one.

All the calculations were carried out by using the Gaussian 98 package.[16] The DFT approach was used with the Becke's three-parameter functional and with the correlation functional of Lee, Yang and Parr (B3LYP). In order to verify the effect of the basis set, the calculations were carried out at two levels of theory: at first, the 6-31G(d) basis set (a split valence basis set supplemented with polarisation d-functions on heavy atoms) was used and subsequently all the stationary points found, were reoptimised with the 6-311+G(d,p) basis set, a triple zeta basis set, plus diffuse functions added to heavy atoms and with polarisation p-functions on hydrogen and 2-d functions on heavy atoms. The ground state structures and transition states for the enantiomerisation of **2b** were fully optimised, with each stationary point found characterised by a frequency calculation. For the structures featuring one imaginary frequency and therefore found to be a saddle point, the normal mode corresponding to the imaginary frequency, was animated by using the Molden visualisation programme.[17] In this way it was verified that the displacements that compose the mode lead to the two enantiomeric structures. The rotational barriers were obtained as the difference between the total energies, including the zero-point and thermal corrections, of the minima and the two transition states.

The results obtained for the energies are reported in Tables 2 and 3 for the B3LYP/6-31G(d), and B3LYP/6-311+G(d,p) calculations. Figure 3 shows all the stationary points found. Two minimum energy structures were found for the non planar ground state of **2b** together with two transition states: (*Z*)-TS and (*E*)-TS.

The two minima are very close in energy (see Tables 2 and 3) and their relative stabilities are reverted by going from the 6-31G(d) basis set to the larger one. From a structural point of view, the two minima essentially differ by the relative positions of the CH_2OCOCH_3 side chain and the *meta*-NH_2 group. At the lower level of

Table 2. Total energies from the DFT calculations on **2b**

	B3LYP/6-31G(d) E,[a] a.u.	B3LYP/6-311+G(d,p) E,[a] a.u.
Minimum 1	−840.896862	−841.141891
Minimum 2	−840.897706	−841.141639
(*Z*)-TS	−840.869137	−841.112564
(*E*)-TS	−840.865477	−841.109153

[a] Zero-point and thermal corrections (at 298.15 K) included.

Table 3. Relative energies obtained from the DFT calculations on **2b**

	B3LYP/6-31G(d) ΔE, kcal mol^{-1}	B3LYP/ 6311+G(d,p) ΔE, kcal mol^{-1}
Minimum 1–minimum 2	0.53	−0.16
(*Z*)-TS-(*E*)-TS	−2.29	−2.14
(*Z*)-TS-minimum 1	17.40	18.40
(*Z*)-TS-minimum 2	17.93	18.24
(*E*)-TS-minimum 1	19.69	20.54
(*E*)-TS-minimum 2	20.22	20.39

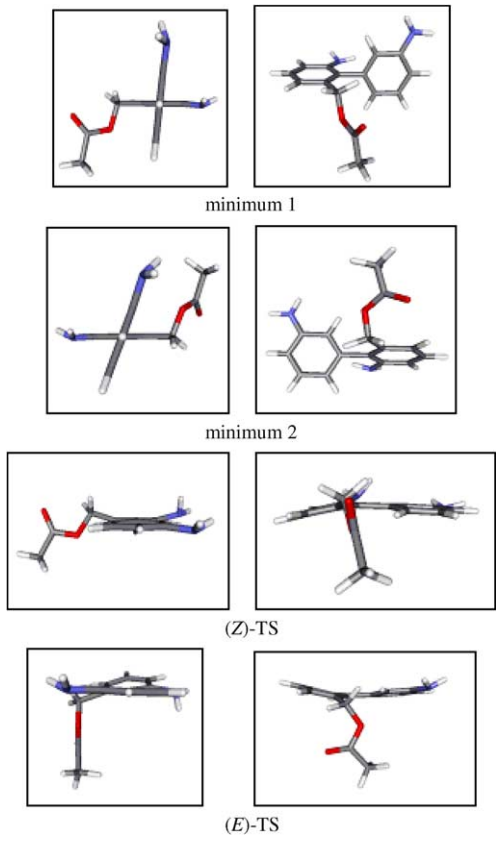

Figure 3. Two orthogonal view of each of the stationary points found for **2b**.

theory the dihedral angle C2–C1–C1′–C2′ between the two phenyl rings was found to be 74.3° in the minimum 1 and −116.2° in minimum 2. With the larger 6-311+G(d,p) basis set, the values were 83.4° and −110.3°, respectively.

The (*Z*)-transition state was found to be more stable than the (*E*) one at both levels of theory. Therefore, with the barriers relative to the (*Z*)-transition state being the lowest, these are the ones to compare with the experimental data. Since two minimum structures were found for compound **2b**, in order to compare the two computed rotational barriers with the experimental one, we had to take into account that both minima 1 and 2 can racemise independently passing through the lowest (*Z*)-transition state. Both processes contribute to the experimentally measured racemisation rate constant. Such a rate constant, under the assumption that the equilibration process between the two minima is fast with respect to the racemisation process, is related to the microscopic rate constants by the Winstein–Holness equation.[18] By using such an equation and under the assumption that $\Delta E \approx \Delta G$, we were able to obtain an 'averaged' rotational barrier that takes into account both processes. Such averaged barriers are reported in Table 4.

Table 4. Rotational barriers relative to the (*Z*)-transition state, averaged according to the Winstein–Holness equation (see text for details)

B3LYP/6-31G(d) ΔE_{WH}, kcal mol^{-1}	B3LYP/6-311+G(d,p) ΔE_{WH}, kcal mol^{-1}
17.72	18.33

In Table 5, the experimental values obtained for the rotational barrier of **2a** are reported together with the computational values obtained for the rotational barrier of **2b**.

The two experimental values for **2a**, obtained by two different techniques at different temperatures, differ by 1.4 kcal mol^{-1} with the value obtained in the micellar aqueous phase by dynamic NMR being the lower one. This can be explained if we keep in mind that a negative value for the ΔS of activation should be expected because in transition states, due to their quasi-planar structure, the rotation of the NH_2 and CH_2OCOR groups may be somewhat restricted. In the micellar phase, due to the specific orientation of the solute, locked by specific interactions with the aggregate, the rotational freedom of the side groups should be lower than in a conventional solvent. Therefore a less negative ΔS of activation should be expected with a corresponding lower barrier, as observed.

Not surprisingly, the computational values obtained at the higher level of theory, are closer to the experimental one obtained in the micellar phase. In fact the computed ones, being obtained as differences of the total energies corrected for the zero-point and thermal corrections differences (at 298.15 K), do not contain the entropic contributions to the barrier.

2.2. Recognition experiments

^{1}H NMR recognition experiments performed in an aqueous solution of biphenylic derivative **1a**, in the presence of surfactants **3** or **4**, did not give any evidence for the recognition phenomena. The spectra relative to aqueous solutions of biphenylic derivative **2a**, in the presence of either surfactants **4a** or **4b** show diastereomeric signals for some aromatic protons. In fact as shown in Figure 4, the aromatic region of the NMR spectrum of an aqueous solution of **2a** in the presence of

Table 5. Rotational barriers of compounds **2** as obtained by experimental and theoretical approaches

Compound	Source	Rotational barrier, kcal mol^{-1}	Solvent, temperature K
2a	Dynamic HPLC	19.7 ± 0.2	Hexane/isopropanol 8/2, 268
2a	Dynamic NMR	18.3 ± 0.2	Micellar aqueous phase, 363
2b	B3LYP/6-31G(d) calculations	17.7	Vacuum, 298
2b	B3LYP/6-311+G(d,p) calculations	18.3	Vacuum, 298

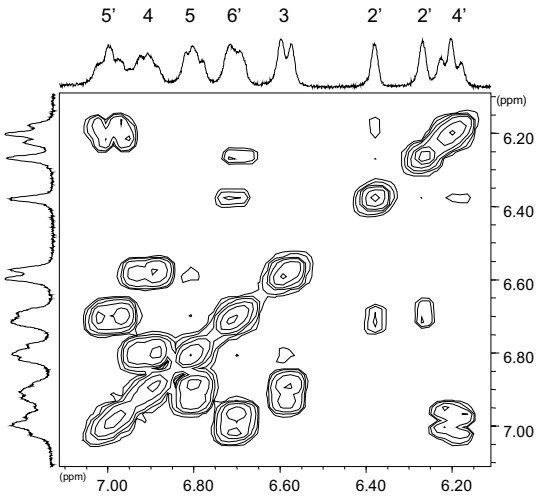

Figure 4. Aromatic region of the H,H-COSY spectrum of an aqueous solution 2.0 mM in **2a** and 10 mM in **4a**.

the aggregates formed by **4a** showed a number of signals and a multiplicity higher than expected. The H,H-COSY experiment as reported in Figure 4 allowed us to assign aromatic protons and thus observe which protons were more influenced by the diastereomeric interactions with the chiral aggregates, that is those at the 2′ and 4′ positions.

In the spectrum of an aqueous solution of biphenylic derivative **2a** in the presence of anionic surfactant **3**, chiral diasteromeric interactions yielded diastereomeric NMR signals only for the enantiomeric protons at the 2′ position (Fig. 5). In all cases (in the presence of the anionic and the cationic surfactants) the intensity ratio of the integrals of diastereomeric signals was 1. As the rotational barrier was such to allow interconversion under the experimental conditions, the absence of deracemisation indicates that there is no appreciable difference in the extent of binding of the enantiomers to the chiral aggregates.

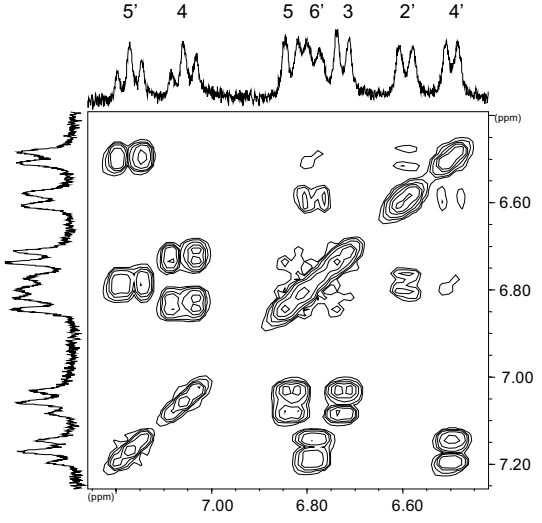

Figure 5. Aromatic region of the H,H-COSY spectrum of an aqueous solution 18 mM in **2a** and 100 mM in **3**.

As far as the NMR experiments are concerned, it is worthwhile to note two points: the first one being that chiral recognition of **2a** enantiomers concerns the same portion of the biphenylic derivative in all the considered aggregates, namely, protons at the 2′ (surfactants **3** and **4**) and 4′ positions (surfactants **4**). The second point is the absence of chiral discrimination of enantiomers of compound **1a** either by the cationic or anionic micelles. The different positions of one of the amino groups on the biphenylic molecule is responsible on one hand for the absence of discrimination of the enantiomers of compound **1a** and on the other hand for the different mode of interaction of the enantiomers of compound **2a**. The amino group on the 3′ position should therefore be responsible for the favourable locking of the solute in the chiral environment of both the cationic and the anionic aggregates.

CD spectra were run on the same solution used in NMR experiments in order to see if in the absence of deracemisation, as demonstrated by NMR experiments, they could put in evidence any induced effect.[19] No chiral effect was observed by CD in any of the aqueous micellar solutions.

3. Conclusion

In conclusion chiral recognition was observed by NMR in chiral micellar aggregates (either cationic or anionic) on racemic mixture of chiral biphenylic derivative **2a**, whereas discrimination was not observed on its regioisomer **1a**. The mode of interaction with the aggregate, and the consequent discrimination, seems therefore dictated by the different position of the amino group.

4. Experimental

NMR spectra were run on a Bruker AC 300 P spectrometer operating at 300.13 and 75.47 MHz for ^{1}H and ^{13}C, respectively, equipped with a sample tube thermostating apparatus. Signals were referenced with respect to TMS ($\delta = 0.000$ ppm) being used as an internal standard in $CDCl_3$ and to DOH ($\delta = 4.750$ ppm at 298 K and $\delta = 4.642$ ppm at 308 K) in D_2O.

^{1}H NMR recognition experiments were performed on aqueous solutions of: (a) 2.0 mM biphenylic derivative **1a** or **2a** in the presence of 10 mM *N*-hexadecyl-*N,N*-dimethyl-*N*-(*S*)-(1-phenyl)ethylammonium bromide **4a** (at 308 K, well above the Krafft point), (b) 6.0 mM biphenylic derivative **1a** or **2a** in the presence of 36 mM *N*-dodecyl-*N,N*-dimethyl-*N*-(*S*)-(1-phenyl)ethylammonium bromide **4b** (at 298 K), (c) 18 mM biphenylic

derivative **1a** or **2a** in the presence of 100 mM **3** (at 298 K). In all cases the ratio between the micellised surfactant and solute was 5.

The dynamic NMR experiments were performed on a Bruker AC 300 P spectrometer. ^{1}H NMR spectra were performed at various temperatures between 295 and 363 K on an aqueous solution of **4a** (10.0 mM) and of **2a** (2.0 mM). The $\Delta\nu$ value between the diastereomeric signals relative to the aromatic protons at the 2′ position in the spectrum registered at 295 K was used in Eq. 1 for obtaining the enantiomerisation rate constant at the coalescence temperature.[23]

CD spectra were registered on a Jasco spectropolarimeter J-715 using quartz cells of 1 and 0.1 cm path length.

Optical rotation measurements were carried out on a Perkin Elmer-241 polarimeter using a cell of 10 cm path length.

HPLC separation of the enantiomers of **1a** and **2a** was carried out on a Chiralpak AD column (250×4.6 mm i.d.). For the dynamic HPLC experiments, the column was placed in a cooling bath with temperature controlled within ±0.2 K while placing a 50 cm long inlet capillary inside the cooling liquid to ensure thermal equilibration of the mobile phase. Retention times for the enantiomers of **1a**: $t_1 = 11$ min, $t_2 = 16$ min using hexane/2-propanol 80/20 as the mobile phase, delivered at 1.0 mL/min, $T = 297$ K. Isolation of the first eluted enantiomer of **1a** for CD characterisation studies was carried out on the same column by three replicate injections of 1 mg/mL (0.5 mL each run) solutions via a 2 mL loop.

Cmc measurements were carried out by isothermal titration microcalorimetry (ITC). In ITC titrations the heat effects accompanying mixing of aliquots of surfactant solution ($m_{surf} \gg$ cmc) with solvent or dilute surfactant solutions were measured in TAM 2277 (*Thermometric, Sweden*) microcalorimeter.

Krafft point and Krafft temperatures of surfactants **4** were measured by conductivity measurements according to a described procedure.[9] Weighted quantities of surfactant **4a** and **4b** were heated to obtain clear solutions. These were kept at 277 K for 24 h before measurement. During measurements the solutions were continually stirred while the temperature was raised at a rate of 0.05 K/min. In the conductivity/temperature plots, the Krafft point was estimated by the first break and the Krafft temperature by the second one. The following values were obtained for **4b**: Krafft point = 295.4 K; Krafft temperature = 304.6 K (20 mM solution). Surfactant **4a** has a Krafft point <277 K.

2-Bromo-3-nitromethylbenzoate was prepared as previously described.[20] Mp 350–351 K. ^{1}H NMR, δ ($CDCl_3$): 3.961 (s, 3H, CH_3), 7.507 (t, 1H, $J_o = 8.0$ Hz), 7.746 (dd, 1H, $J_m = 1.6$ Hz, $J_o = 8.0$ Hz), 7.838 (dd, 1H, $J_m = 1.6$ Hz, $J_o = 8.0$ Hz). ^{13}C NMR, δ ($CDCl_3$): 53.07, 112.72, 126.64, 128.19, 135.71, 151.93, 165.49.

2-Carboxymethyl-2′,6-dinitrobiphenyl. 2-Bromo-3-nitromethylbenzoate (0.5 g, 4 mmol) and 1.0 g of 1-iodo-2-nitrobenzene (2 mmol) were added to 10 mL of dry DMF. To the reaction mixture, heated at 353 K in an inert atmosphere, 1.0 g of finely powdered Cu (Fluka) was added while stirring. The reaction was monitored by TLC until the disappearance of 1-iodo-2-nitrobenzene. The reaction mixture was then allowed to cool and filtered. After removal of the solvent in vacuum, the residue was diluted with CH_2Cl_2. The organic solution was washed with water, aqueous ammonia solution (10%), brine and then dried over Na_2SO_4. Purification on silica gel using hexane/Et_2O/CH_2Cl_2 (10:5:1) as eluent yielded 350 mg (59%) of a yellow solid. Mp 408–411 K. ^{1}H NMR, δ ($CDCl_3$): 3.616 (s, CH_3, 3H), 7.11–7.15 (m, ar, 1H), 7.56–7.65 (m, ar, 2H), 7.580 (t, ar, 1H, $J_o = 8.2$ Hz, $J_o = 7.9$ Hz), 8.218 (dd, ar, 1H, $J_o = 7.9$ Hz, $J_m = 1.4$ Hz), 8.275 (dd, ar, 1H, $J_o = 8.2$ Hz, $J_m = 1.4$ Hz), 8.29–8.34 (m, ar, 1H). ^{13}C NMR, δ ($CDCl_3$): 52.54, 124.47, 127.76, 128.73, 129.22, 129.49, 131.20, 131.84, 133.40, 134.66, 134.83, 147.82, 148.64, 165.04.

2-Carboxy-2′,6-dinitrobiphenyl. 2-Carboxymethyl-2′,6-dinitrobiphenyl (0.5 g, 1.65 mmol) was added to 20 mL of ethanol and 10 mL of an aqueous solution of NaOH (5%). After 3 h under reflux and stirring, the reaction mixture was allowed to cool and was acidified with HCl (1.0 M). The mixture was extracted with $CHCl_3$ and the organic layer washed with brine and dried over Na_2SO_4. Removal of chloroform by rotary evaporation yielded 0.46 g (97%) of a low melting yellow solid. ^{1}H NMR, δ ($CDCl_3$): 7.085 (d, ar, 1H, $J_o = 6.8$ Hz), 7.57–7.64 (m, ar, 2H), 7.658 (t, ar, 1H, $J_o = 8.1$ Hz), 8.220 (d, ar, 1H, $J_o = 8.1$ Hz), 8.27–8.33 (m, ar, 2H). ^{13}C NMR, δ ($CDCl_3$): 124.62, 128.78, 128.85, 129.39, 129.41, 131.52, 133.63, 135.45, 147.81, 148.85, 169.60.

2-Hydroxymethyl-2′,6-dinitrobiphenyl. B_2H_6 in THF (2 mL, 1 M) solution were added dropwise to a solution of 0.2 g (0.7 mmol) of 2-carboxy-2′,6-dinitrobiphenyl in 3 mL of dry THF, while stirring in an inert atmosphere. After two hours at room temperature, the reaction mixture was treated with wet THF, until the development of H_2, and then brine. Removal of the solvent from the organic layer yielded 0.2 g (92%) of brown oil. ^{1}H NMR, δ ($CDCl_3$): 4.292 (s, CH_2, 2H), 7.20 (dd, ar, 1H, $J_o = 7.4$ Hz, $J_m = 1.4$ Hz), 7.56–7.70 (m, ar, 3H), 7.86 (d, ar, 1H, $J_o = 8.0$ Hz), 8.05 (dd, ar, 1H, $J_o = 8.0$ Hz, $J_m = 1.3$ Hz), 8.23 (dd, ar, 2H, $J_o = 7.8$ Hz, $J_m = 1.4$ Hz). ^{13}C NMR, δ ($CDCl_3$): 62.21, 123.57, 124.85, 128.93, 129.47, 130.47, 130.85, 131.91, 132.45, 133.71, 140.85, 147.43, 147.80.

2,2′-Dinitro-6-(octanoyloxymethyl)biphenyl. Octanoyl chloride (120 μL, 0.7 mmol) and 60 μL of pyridine were added, while stirring at room temperature, to 0.2 g (0.7 mmol) of 2-hydroxymethyl-2′,6-dinitrobiphenyl in 15 mL of CH_2Cl_2. After 48 h, the reaction mixture was washed with an aqueous solution of HCl (1.0 M) and then a saturated aqueous solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4. After removal of solvent, purification of the residue on silica gel, using Et_2O/$CHCl_3$ (60:40) as eluent, yielded 0.24 g (80%) of

yellow oil. ^{1}H NMR, δ ($CDCl_3$): 0.836 (t, CH_3, 3H, $J = 5.8$ Hz), 1.238 (m, aliphatic chain, 10H), 1.638 (m, CH_2, 2H), 2.429 (t, $CH_2\alpha$, 2H, $J = 7.3$ Hz), 4.57–4.85 (AB system, CH_2OCO, 2H, $J = 13.0$ Hz), 7.242 (dd, ar, 1H, $J_o = 7.0$ Hz, $J_m = 1.3$ Hz), 7.58–7.75 (m, ar, 3H), 7.774 (dd, ar, 1H, $J_o = 7.7$ Hz, $J_m = 1.3$ Hz), 8.132 (d, ar, 1H, $J_o = 8.2$ Hz, $J_m = 1.3$ Hz), 8.275 (dd, ar, 1H, $J_o = 8.2$ Hz, $J_m = 1.3$ Hz).

2,2′-Diamino-6-(octanoyloxymethyl)biphenyl **1a**. $SnCl_2 \cdot 2H_2O$ (0.57 g, 2.5 mmol) was added to 0.10 g (0.25 mmol) of 2,2′-dinitro-6-(octanoyloxymethyl) biphenyl in 10 mL of absolute ethanol. After 2 h while stirring at 343 K, the reaction mixture was poured into a beaker with ice and made alkaline with NaOH (12.0 M). The aqueous solution was extracted with ethyl acetate and the organic layer dried over Na_2SO_4. After removal of solvent, purification of the residue on silica gel, using ethyl acetate/hexane (70:30) as eluent, yielded the target product (58%). ^{1}H NMR, δ ($CDCl_3$): 0.870 (t, CH_3, 3H. $J = 6.5$ Hz), 1.250 (m, chain, 10H), 1.556 (m, $CH_2\beta$, 2H), 2.243 (t, $CH_2\alpha$, 2H, $J = 7.4$ Hz), 3.538 (s, NH, 4H), 4.793 (AB system, CH_2 OCO, 2H, $J = 12.9$ Hz), 6.73–6.83 (m, ar, 3H), 6.850 (d, ar, 1H, $J_o = 7.5$ Hz), 6.993 (d, ar, 1H, $J_o = 7.5$ Hz), 7.090 (t, ar, 1H, $J_o = 7.6$ Hz), 7.100 (t, ar. 1H, $J_o = 7.5$ Hz).^{13}C NMR, δ ($CDCl_3$): 14.05, 22.56, 24.86, 28.89, 29.06, 31.62, 34.23, 64.47, 115.10, 115.60, 118.39, 118.89, 128.70, 129.96, 130.80, 135.94, 144.42, 144.84, 173.42. ES-MS = 341 (MH^+).

2-Carboxymethyl-3′,6-dinitrobiphenyl. 2-Bromo-3-nitromethylbenzoate (1.0 g, 8.0 mmol) and 1.0 g (2.0 mmol) of 1-iodo-3-nitrobenzene were coupled according to the above described Ulmann procedure (preparation of 2-carboxymethyl-2′,6-dinitrobiphenyl). The final residue was purified on silica gel, using hexane/Et_2O/toluene (50:40:10), and yielded a white solid (34%) mp = 380–384 K. ^{1}H NMR, δ ($CDCl_3$): 7.51–7.58 (m, ar, 2H), 7.645 (t, ar, 1H, $J_o = 8.0$ Hz), 8.000 (dd, ar, 1H, $J_o = 8.0$ Hz, $J_m = 1.3$ Hz), 8.074 (t, ar, 1H, $J_m = 1.2$ Hz), 8.145 (dd, ar, 1H, $J_o = 8.0$ Hz, $J_m = 1.3$ Hz) 8.234 (m, ar, 1H, $J_o = 6.9$ Hz). ^{13}C NMR, δ ($CDCl_3$): 52.62, 123.18, 123.37, 126.79, 129.49, 133.09, 133.57, 133.78, 134.39, 136.67, 147.74, 150.35, 165.52.

2-Carboxy-3′,6-dinitrobiphenyl. 2-Carboxymethyl-3′,6-dinitrobiphenyl (0.5 g, 1.65 mmol) was hydrolysed as above described for 2-carboxy-2′,6-dinitrobiphenyl. Removal of the solvent by rotary evaporation yielded a white low melting solid (97%). ^{1}H NMR, δ ($CDCl_3$): 7.45–7.61 (m, ar, 2H), 7.682 (t, ar, 1H, $J_o = 8.1$ Hz), 8.042 (dd, ar, 1H, $J_o = 8.1$ Hz, $J_m = 1.2$ Hz), 8.077 (t, ar, 1H, $J_m = 0.9$ Hz), 8.22–8.26 (m, ar, 2H).

2-Hydroxymethyl-3′,6-dinitrobiphenyl. 2-Carboxy-3′,6-dinitrobiphenyl (0.2 g, 0.7 mmol) was reduced as above described for 2-hydroxymethyl-2′,6-dinitrobiphenyl. Work up of the reaction yielded 0.18 g (92%) of brown oil. ^{1}H NMR, δ ($CDCl_3$): 4.362 (m, CH_2, 2H), 7.50–7.68 (m, ar, 4H), 7.901 (d, ar, 1H, $J_o = 7.9$ Hz), 8.101 (t, ar, 1H, $J_m = 1.7$ Hz); 8.260 (dd, ar, 1H, $J_o = 8.0$ Hz, $J_m = 1.7$ Hz, $J_m = 0.8$ Hz). ^{13}C NMR, δ ($CDCl_3$): 151.99, 62.04, 65.84, 123.25, 123.63, 129.50, 129.62, 132.01, 134.72, 136.54, 141.51, 148.16, 149.27.

2,3′-Dinitro-6-(octanoyloxymethyl)biphenyl. 2-Hydroxymethyl-3′,6-dinitrobiphenyl (0.2 g, 0.7 mmol) was esterified with octanoyl chloride according to the procedure described for 2,2′-dinitro-6-(octanoyloxymethyl)biphenyl. The residue was purified on silica gel, using $CHCl_3$ as eluent, and yielded a yellow oil (80%). ^{1}H NMR, δ ($CDCl_3$): 0.858 (t, CH_3, 3H, $J = 6.8$ Hz), 1.243 (m, CH_2, 10H), 2.274 (t, CH_2, 2H, $J = 7.4$ Hz), 4.802 (AB system, CH_2, 2H, $J = 13.0$ Hz), 7.54–7.66 (m, ar, 3H), 7.776 (dd, ar, 1H, $J_o = 8.0$ Hz, $J_m = 1.2$ Hz), 7.956 (d, ar, 1H, $J_o = 8.0$ Hz, $J_m = 1.2$ Hz), 8.152 (t, ar, 1H, $J_m = 1.8$ Hz, $J_m = 2.2$ Hz), 8.294 (dd, ar, 1H, $J_o = 8.0$ Hz $J_m = 1.5$ Hz, $J_m = 2.2$ Hz).

2,3′-Diamino-6-(octanoyloxymethyl)biphenyl **2a**. 2,3′-Dinitro-6-(octanoyloxymethyl)biphenyl (0.1 g, 0.25 mmol) was reduced according to the procedure reported for 2,2′-diamino-6-(octanoyloxymethyl)biphenyl. The residue was purified on silica gel, using $CHCl_3$ as the eluent, and yielded a yellow oil (13%). ^{1}H NMR, δ ($CDCl_3$): 0.866 (t, CH_3, 3H, $J = 6.5$ Hz), 1.258 (m, CH_2 chain, 8H), 1.575 (m, $CH_2\beta$, 2H), 2.256 (t, $CH_2\alpha$, 2H, $J = 7.4$ Hz), 3.632 (s, NH, 1H), 4.813 (s, CH_2OCO, 2H), 6.557 (t, ar, 1H, $J_m = 1.5$ Hz, $J_m = 1.8$ Hz), 6.622 (dd, ar, 1H $J_o = 7.7$ Hz, $J_m = 2.4$ Hz), 6.667 (dd, ar, 1H, $J_o = 8.0$ Hz, $J_m = 2.4$ Hz), 6.721 (d, ar, 1H, $J_o = 8.0$ Hz), 6.830 (d, ar, 1H, $J_o = 8.0$ Hz), 7.137 (t, ar, 1H, $J_o = 8.0$ Hz), 7.210 (t, ar, 1H, $J_o = 8.0$ Hz). ^{13}C NMR, δ ($CDCl_3$): 14.11, 22.63, 24.99, 28.99, 31.69, 34.39, 64.49, 114.53, 114.95, 116.23, 118.40, 119.96, 127.57, 128.23, 130.11, 134.79, 137.42, 144.27, 144.96, 147.03, 173.55. ES-MS = 341 (MH^+).

(S)-N,N-Dimethyl-N-hexadecyl-N-(1-phenyl)ethylammonium bromide **4a**. (*S*)-*N,N*-dimethyl-α-methylbenzylamine was quaternised with 1-bromohexadecane according to a reported procedure.[8] ^{1}H NMR, δ ($CDCl_3$): 0.833 (t, CH_3, 3H, $J = 6.5$ Hz), 1.249 (m, CH_2 chain, 26H), 1.783 (m, CH_2, 2H), 1.830 (d, CH_3, 3H, $J = 7.1$ Hz), 3.160 (s, CH_3, 3H), 3.200 (s, CH_3, 3H), 3.470 (t, CH_2, 2H, $J = 7.1$ Hz), 5.389 (q, CH, 1H, $J = 7.1$ Hz), 7.38–7.47 (m, ar, 3H), 7.620 (m, ar, 2H). $[\alpha]_D^{20}$ −19 (*c* 10, EtOH). cmc = 0.24 mmol/kg.

(S)-N,N-Dimethyl-N-dodecyl-N-(1-phenyl)ethylammonium bromide **4b**. (*S*)-*N,N*-Dimethyl-α-methylbenzylamine was quaternised with 1-bromododecane according to a reported procedure.[8] ^{1}H NMR, δ ($CDCl_3$): 0.864 (t, CH_3, 3H, $J = 6.5$ Hz), 1.233 (m, CH_2 chain, 16H), 1.326 (m, CH_2 2H), 1.767 (m, CH_2, 2H), 1.826 (d, CH_3, 3H, $J = 7.1$ Hz), 3.133 (s, CH_3, 3H), 3.175 (s, CH_3, 3H), 3.497 (t, CH_2, 2H, $J = 7.1$ Hz), 5.488 (q, CH, 1H, $J = 7.1$ Hz), 7.36–7.46 (m, ar, 3H), 7.590 (m, ar, 2H). Elemental analysis C 66.30%; H 10.16%; N 3.69% (expected C 66.31%; H 10.12%; N 3.52%). $[\alpha]_D^{20}$ −21.6 (*c* 9.8, EtOH). cmc = 7.7 mmol/kg.

Sodium-N-dodecanoyl-L-prolinate **3** was prepared and characterised as previously reported.[7]

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